Total Synthesis of Quinolizidine (−)-217A. Application of Iminoacetonitrile Cycloadditions in Organic Synthesis

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Supporting Information

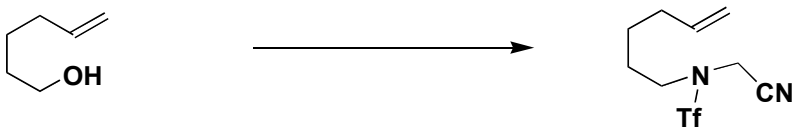
General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and tetrahydrofuran were purified by pressure filtration through activated alumnia. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Piperidine, triethylamine, diisopropylethylamine, and hexamethyldisilazane were distilled under argon from calcium hydride. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). NaI and LiBr were dried under vacumm (0.1 mmHg) at 70 ºC for 24 h. *n*-Butyllithium was titrated in tetrahydrofuran with BHT using 1,10-phenanthroline as the indicator.[1]

Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with an Inova 500, Inova 300, and Bruker 400 spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from

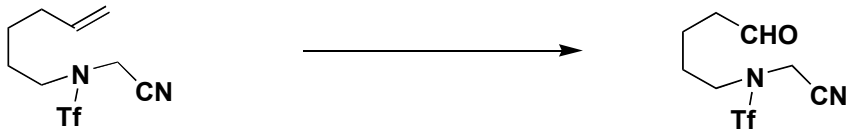
[1] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 9, 165

tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.



11 **12**

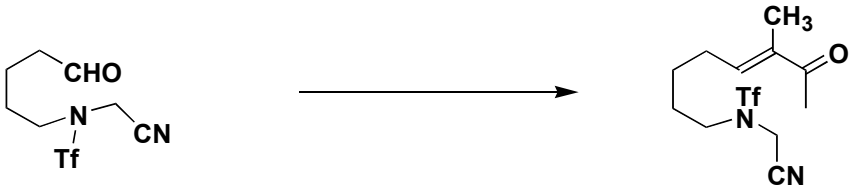
***N*-(Cyanomethyl)-*N*-(5-hexenyl)trifluoromethanesulfonamide (12).** A 500-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with triphenylphosphine (15.711 g, 59.9 mmol), 80 mL of THF, and $TfNHCH_2CN$ (10.330 g, 54.91 mmol). 5-Hexen-1-ol (6.00 mL, 5.00 g, 49.9 mmol) was then added in one portion followed by dropwise addition of DIAD (11.60 mL, 12.11 g, 59.9 mmol) over 20 min. The resulting mixture was stirred at rt for 2 h and then concentrated to give 43.11 g of a yellow solid. A solution of this material in CH_2Cl_2 was concentrated onto 30 g of silica gel and transferred to the top of a column of 100 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes yielded 12.357 g (92%) of **12** as a colorless oil: IR (film): 3081, 2997, 2942, 2866, 1642, 1393, 1355, 1296, 1271, 1231, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.1, 10.1, 6.7 Hz, 1 H), 5.01-5.08 (m, 2H), 4.35 (br s, 2 H), 3.55 (br s, 2 H), 2.13 (app q, J = 7.0 Hz, 2 H), 1.72 (quint, J = 7.6 Hz, 2 H), 1.47 (quint, J = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 119.8 (q, J = 322 Hz), 115.8, 113.4, 49.3, 35.8, 33.0, 26.7, 25.3; Anal. Calcd for $C_9H_{13}F_3N_2O_2S$: C, 40.00; H, 4.85; N, 10.36. Found: C, 39.62; H, 4.81; N, 10.22.



12 **13**

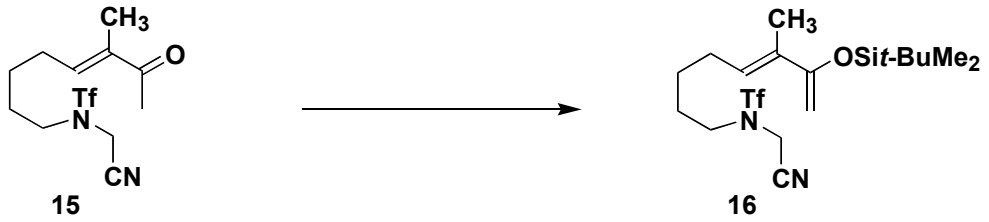
***N*-(Cyanomethyl)-*N*-(5-hexanal)trifluoromethanesulfonamide (13).** A 200-mL, recovery flask containing triflamide **12** (5.808 g, 21.49 mmol) was fitted with a rubber septum and argon-inlet needle and purged with argon. CH_2Cl_2 (80 mL) was added, and the flask was cooled at -78 °C while ozone was bubbled through the solution for 25 min. The resulting blue solution was degassed with a stream of argon for 10 min. Triphenylphosphine (5.918 g, 22.56 mmol) was added, and the solution

was allowed to slowly warm to rt over 16 h. Concentration by rotary evaporation afforded 12.09 g of a cloudy, white oil. A solution of this material in CH_2Cl_2 was concentrated onto 24 g of silica gel and transferred to the top of a column of 110 g of silica gel. Elution with 25% EtOAc-hexanes provided 5.359 g (92%) of **13** as a colorless oil: IR (film): 2997, 2954, 2877, 2838, 2735, 1723, 1467, 1394, 1360, 1294, 1269, 1229, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, J = 1.0 Hz, 1 H), 4.39 (br s, 2 H), 3.57 (br s, 2 H), 2.59 (t, J = 6.4 Hz, 2 H), 1.69-1.78 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 119.7 (q, J = 322 Hz), 113.5, 49.1, 42.8, 35.7, 26.4, 18.2; Anal. Calcd for $C_8H_{11}F_3N_2O_3S$: C, 35.29; H, 4.07; N, 10.29. Found: C, 35.42; H, 4.02; N, 10.30.

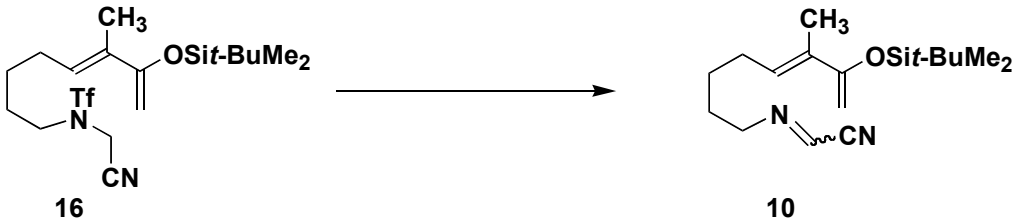


13 **15**

***N*-(Cyanomethyl)-*N*-(6-methyl-(*E*)-5-octen-7-one)trifluoromethanesulfonamide (15).** A 300-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aldehyde **13** (7.394 g, 27.16 mmol) and 54 mL of toluene. 3-(Triphenylphosphoranylidene)butan-2-one **14** (10.010 g, 30.12 mmol) was then added in one portion, and the rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter. The reaction mixture was heated at 70 °C for 7 h. Concentration by rotary evaporation afforded 17.92 g of a brown oil. A solution of this material in CH_2Cl_2 was concentrated onto 30 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 20-30% EtOAc-hexanes provided 7.686 g (87%) of **15** as a yellow oil: IR (neat): 2994, 2945, 2869, 1735, 1666, 1396, 1230, 1195, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (td, J = 7.3, 1.2 Hz, 1 H), 4.38 (br s, 2 H), 3.58 (br s, 2 H), 2.33 (m, 5 H), 1.78 (m, 5 H), 1.57 (app quint, J = 7.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 141.6, 138.6, 113.9, 49.5, 36.2, 28.7, 27.5, 26.0, 25.5, 11.8; Anal. Calcd for $C_{12}H_{17}F_3N_2O_3S$: C, 44.17; H, 5.25; N, 8.58. Found: C, 43.95; H, 5.27; N, 8.84.

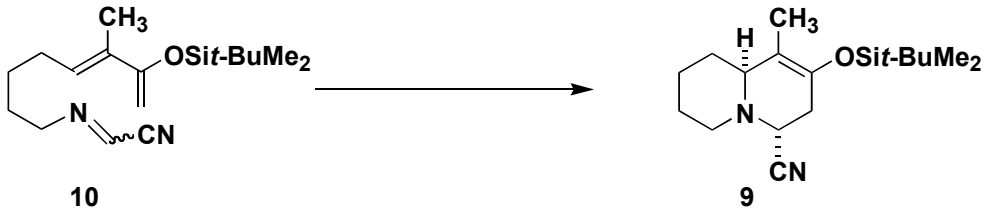


***N*-(Cyanomethyl)-*N*-(7-(*tert*-butyldimethylsiloxy)-6-methyl-(*E*)-5,7-octadienyl)trifluoromethanesulfonamide (16).** A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NaI (6.254 g, 41.72 mmol), a solution of enone **15** (9.076 g, 27.81 mmol) in 60 mL of CH_3CN, and Et_3N (5.86 mL, 4.22 g, 41.7 mmol). *tert*-Butyldimethylsilyl chloride (4.611 g, 30.59 mmol) was added in one portion, and the resulting mixture was stirred at rt in the dark for 18 h. The reaction mixture was then diluted with 50 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 30 mL of 1M NaOH solution, 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 12.37 g of a yellow oil. Column chromatography on 150 of acetone-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 11.814 g (96%) of **16** as a yellow oil: IR (film): 3127, 2933, 2860, 1645, 1596, 1464, 1398, 1231, 1197 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (t, J = 7.3 Hz, 1 H), 4.43 (s, 1 H), 4.28-4.44 (br s, 2 H), 4.24 (s, 1 H), 3.55 (br s, 2 H), 2.20 (app q, J = 7.3 Hz, 2 H), 1.77 (s, 3 H), 1.73 (app quint, J = 7.3 Hz, 2 H), 1.47 (app quint, J = 7.6 Hz, 2 H), 0.98 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 132.2, 127.0, 119.8 (q, J = 322 Hz), 113.3, 91.7, 49.4, 35.8, 27.6, 27.2, 26.1, 25.9, 18.5, 13.5, -4.4; Anal. Calcd for $C_{18}H_{31}F_3N_2O_3SSi$: C, 49.07; H, 7.09; N, 6.36. Found: C, 48.82; H, 6.99; N, 6.55.

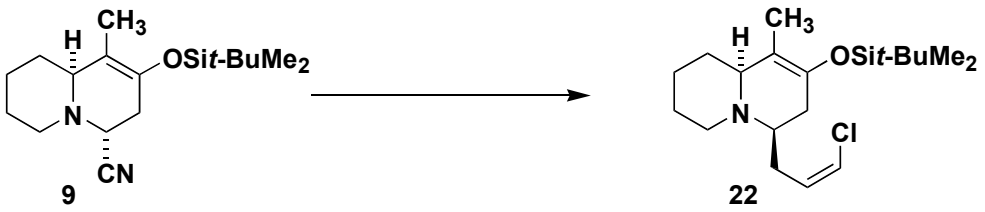


7-(*tert*-Butyldimethylsiloxy)-6-methyl-(*E*)-5,7-octadienyliminoacetonitrile (10). A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (19.65 g, 60.3 mmol) and 60 mL of THF. A solution of triflamide **16** (6.643 g, 15.08 mmol) in 15 mL of THF was then added in one portion, and the reaction mixture was heated at 55 °C for 1.5 h. The resulting mixture was allowed to cool to rt and then diluted with 100 mL of water. The aqueous layer was separated and extracted with three 55-mL portions of ether, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give

5.88 g of a yellow oil. Column chromatography on 25 g of acetone-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) afforded 4.160 g (90%) of **10** (84:16 mixture of *E* and *Z* imine isomers by ^1H NMR analysis) as a colorless oil: IR (film): 2931, 2859, 1644, 1595, 1472, 1463, 1362, 1255 cm^{-1}; For the *Z* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J= 2.1 Hz, 1 H), 6.00 (app t, J = 7.6 Hz, 1 H), 4.42 (s, 1 H), 4.26 (s, 1 H), 3.85 (td, J = 7.0, 2.1 Hz, 2 H), 2.16 (app q, J = 7.6 Hz, 2 H), 1.69-1.76 (m, 5 H), 1.41-1.57 (m, 2 H), 0.97 (m, 9 H), 0.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 131.7, 131.5, 127.9, 114.7, 91.5, 59.9, 29.9, 27.9, 27.2, 26.1, 18.6, 13.5, -4.4. For the *E* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 1.5 Hz, 1 H), 6.00 (app t, J = 7.6 Hz, 1 H), 4.42 (s, 1 H), 4.26 (s, 1 H), 3.66 (td, J = 6.7, 1.5 Hz, 2 H), 2.16 (app q, J = 7.6 Hz, 2 H), 1.69-1.76 (m, 5 H), 1.41-1.57 (m, 2 H), 0.97 (m, 9 H), 0.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 135.9, 131.7, 127.8, 114.7, 91.5, 63.2, 29.8, 28.0, 27.3, 26.1, 18.6, 13.5, -4.4; Anal. Calcd for $C_{17}H_{30}N_2OSi$: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.43; H, 9.96; N, 9.11.



2-(*tert*-Butyldimethylsiloxy)-1-methyl-*cis*-1,2-didehydro-4-cyanoquinolizidine (9). A threaded Pyrex tube (ca. 350-mL capacity) equipped with a rubber septum and argon inlet needle was charged with BHT (9.30 g, 42.2 mmol), imine **10** (4.312 g, 14.07 mmol), and 175 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 130 °C oil bath for 36 h and then allowed to cool to rt. Concentration by rotary evaporation afforded 13.71 g of a yellow oil. A solution of this material in CH_2Cl_2 was concentrated onto 25 g of acetone-deactivated silica gel and transferred to the top of a column of 180 g of acetone-deactivated silica gel. Elution with 1% Et_3N-7% EtOAc-hexanes provided 2.415 g (56%) of **9** as a white solid: mp 74-77 ºC; IR (CH_2Cl_2): 2938, 2857, 2760, 1686, 1462, 1382, 1359, 1295, 1253, 1195, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (dd, J = 5.5, 1.2 Hz, 1 H), 2.73-2.79 (m, 3 H), 2.52 (td, J = 11.9, 3.1 Hz, 1 H), 2.17 (dd, J = 15.6, 1.2 Hz, 1 H), 1.98-2.01 (m, 1 H), 1.82-1.85 (m, 1 H), 1.57-1.71 (m, 2 H), 1.56 (s, 3 H), 1.33-1.42 (m, 1 H), 1.08-1.17 (m, 1 H), 0.95 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 117.2, 113.7, 60.5, 54.6, 53.3, 34.2, 30.4, 26.1, 25.9, 24.9,18.5, 2.4, -3.5; Anal. Calcd for $C_{17}H_{30}N_2OSi$: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.74; H, 9.80; N, 9.08.

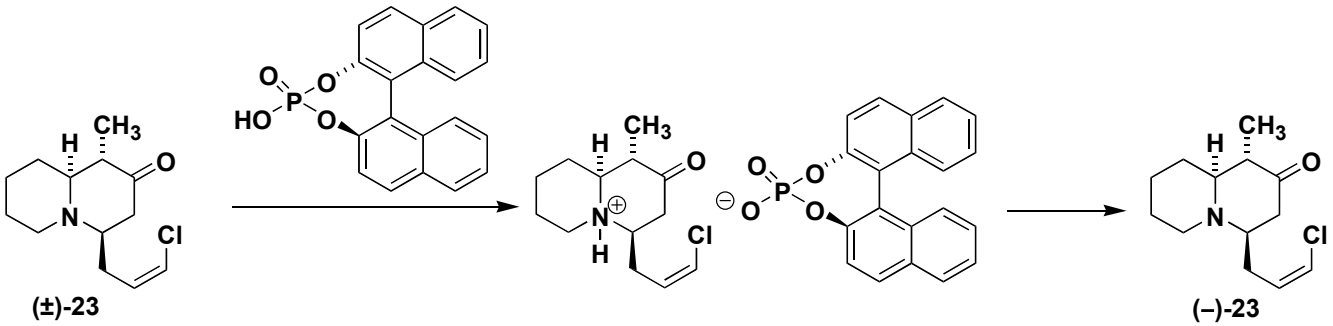


2-(*tert*-Butyldimethylsiloxy)-1-methyl-*trans*-1,2-didehydro-4-(3-chloro-(*Z*)-2-propene)quinolizidine (22). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (1.68 mL, 1.28 g, 7.9 mmol) and 10 mL of THF. The solution was cooled at 0 °C while 3.38 mL of *n*-BuLi solution (2.35 M in hexane, 7.9 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **9** (1.015 g, 3.31 mmol) in 5 mL of THF was added dropwise via cannula over 5 min. The resulting solution was stirred at -78 °C for 3.5 h, and then a precooled (-78 °C) solution of 3-bromo-1-chloropropene (1.234 g, 7.94 mmol) in 5 mL of THF was added dropwise via cannula over 1 min. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to 0 °C and stirred for an additional hour. The reaction mixture was diluted with 80 mL of ether and 30 mL of water. The aqueous layer was extracted with three 25-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 1.917 g of an orange oil that was used immediately in the next step without further purification.

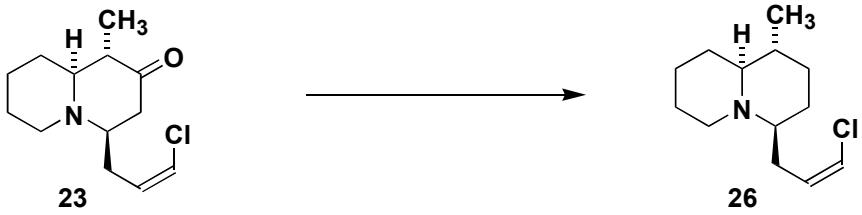
A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with $NaBH_3CN$ (0.832 g, 13.24 mmol) and 10 mL of acetonitrile. Acetic acid (1.52 mL, 1.59 g, 26.5 mmol) was added dropwise via syringe over 4 min. The resulting solution was stirred at rt for 30 min, and then a solution of the α-amino nitrile (1.917 g) prepared in the previous step in 8 mL of acetonitrile was added over 3 min by cannula. The reaction mixture was stirred at rt for 2 h and then diluted with 35 mL of water and 35 mL of dichloromethane. The aqueous layer was separated and extracted with three 25-mL portions of dichloromethane, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated onto 3.5 g of silica gel. The free-flowing powder was placed at the top of a column of 60 g of silica gel and eluted with 15% EtOAc-hexanes (containing 1% Et_3N) to provide 0.902 g (77%) of the quinolizidine **22** as a yellow oil: IR (neat): 2931, 2857, 2791, 2741, 1698, 1629, 1472, 1362, 1257, 1195 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (app d, J = 6.60 Hz, 1 H), 5.86 (app q, J = 7.05 Hz, 1 H), 3.13 (app d, J = 11.21 Hz, 1 H), 2.40-2.54 (m, 4 H), 2.16-2.23 (m, 1 H), 1.90-2.01 (m, 3 H), 1.53-1.71 (m, 6 H), 1.20-

1.34 (m, 2 H), 0.95 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 129.2, 120.6, 113.2, 65.8, 58.6, 36.7, 31.0, 30.6, 26.4, 26.2, 24.8, 18.5, 12.4, -3.5, -3.9; Anal. Calcd for $C_{19}H_{34}ClNOSi$: C, 64.10; H, 9.63; N, 3.93. Found: C, 64.25; H, 10.62; N, 4.03.

1-Methyl-*trans*-1,2-didehydro-4-(3-chloro-(*Z*)-2-propene)quinolizidin-2-one (23). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with silyl enol ether **22** (1.60 g, 4.5 mmol) and 20 mL of THF. The reaction mixture was cooled at -78 °C while 4.94 mL of TBAF solution (1.0 M in THF, 4.9 mmol) was added dropwise via syringe over 2 min. The resulting solution was stirred at -78 °C for 1.5 h and then the reaction mixture was diluted with 35 mL of ether and 15 mL of water. The aqueous layer was separated and extracted with three 20-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated onto 3 g of silica gel. The free-flowing powder was placed at the top of a column of 25 g of silica gel and eluted with 15% EtOAc-1% Et_3N-hexanes to provide 0.951 g (88%) of the ketone **23** as a yellow oil: IR (neat): 2934, 2859, 2794, 1718, 1629, 1443, 1337, 1237, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 (d, J = 7.3 Hz, 1 H), 5.87 (app q, J = 7.0 Hz, 1 H), 3.24 (app d, J = 11.3 Hz, 1 H), 2.46-2.59 (m, 4 H), 2.33-2.38 (m, 2 H), 1.89-1.97 (m, 3 H), 1.70-1.78 (m, 2 H), 1.57 (qt, J = 12.8, 3.7 Hz, 1 H), 1.24-1.40 (m, 2 H), 1.01 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 127.1, 120.7, 68.5, 62.8, 50.6, 49.4, 46.4, 31.7, 31.4, 26.0, 24.0, 10.4; Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.79; H, 8.13; N, 6.14.

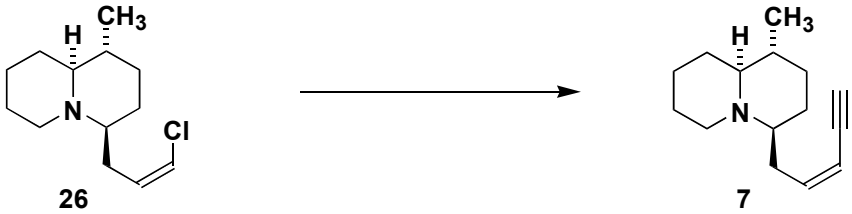


(1*R*, 4*S*, 9a*S*)-1-Methyl-*trans*-1,2-didehydro-4-(3-chloro-(*Z*)-2-propene)quinolizidin-2-one (23). A 100-mL, one-necked, pear-shaped flask was charged with the ketone (±)-**23** (0.430 g, 1.78 mmol), (*R*)-(–)-1,1′-binaphthyl-2,2′-diylphosphoric acid (0.681 g, 1.96 mmol), 10 mL of CH_2Cl_2, and 25 mL of methanol. The reaction mixture was heated at 50 °C for 10 min and then allowed to cool to rt. The reaction mixture was concentrated to a volume of ca. 10 mL and then placed in a freezer at -18 °C for 15 h. The resulting crystals were collected on a sintered funnel and air-dried to yield 0.364 g of white solid. Recrystallization of the solid obtained from the mother liquor from 25 mL of methanol afforded 0.132 g of a white solid. The two crops of crystals were combined and treated with 30 mL of EtOAc and 15 mL of 10% ammonium hydroxide solution. The aqueous layer was separated and extracted with three 20-mL of portions EtOAc, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.189 g (44% from (±)-**23**; i.e., 88% of theoretical) of ketone (-)-**23** as a yellow oil: $[\alpha]_D^{22}$ -42 (*c* 2.76, $CHCl_3$). Resolution with (*S*)-(+)-1,1′-binaphthyl-2,2′-diylphosphoric acid using the same procedure provided (+)-**23** in 43% yield.



(1*R*, 4*S*, 9a*S*)-1-Methyl-*trans*-1,2-didehydro-4-(3-chloro-(*Z*)-2-propene)quinolizidine (26). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ketone **23** (0.184 g, 0.76 mmol), TsOH (0.045 g, 0.26 mmol), 1.5 mL of DMF, and 1.5 mL of sulfolane. The reaction mixture was heated at 110 °C for 2 h. $NaBH_3CN$ (0.191 g, 3.04 mmol), *t*-BuSH (1.29 mL, 1.03 g, 11.4 mmol), and 3 mL of cyclohexane were added in one portion and the resulting mixture was heated at 110 °C for 5 h. The reaction mixture was allowed to cool to rt and then diluted with 15 mL of ether and 40 mL of water. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with

10 mL of water, 10 mL of satd $NaHCO_3$ solution, 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.29 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 0-20% EtOAc-1% Et_3N-hexanes) afforded 0.144 g (66%) of the quinolizidine **26** as a pale, yellow oil: $[\alpha]_D^{22}$ -60 (*c* 2.4, $CHCl_3$); IR (film): 2928, 2852, 2787, 2754, 1628, 1442, 1376, 1331, 1305, 1264 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (dt, J = 7.1 Hz, 1.7 Hz, 1 H), 5.88 (q, J = 7.0 Hz, 1 H), 3.24 (app d, J = 11.0 Hz, 1 H), 2.42-2.49 (m, 2 H), 2.04-2.08 (m, 1 H), 1.90-1.94 (m, 1 H), 1.60-1.78 (m, 5 H), 1.45-1.53 (m, 3 H), 1.03-1.33 (m, 4 H), 0.86 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 119.4, 69.8, 62.9, 52.1, 36.7, 34.2, 32.2, 32.1, 30.6, 26.6, 25.0, 19.6; Anal. Calcd for $C_{13}H_{22}ClN$: C, 68.55; H, 9.74; N, 6.15. Found: C, 68.49; H, 9.72; N, 6.12.



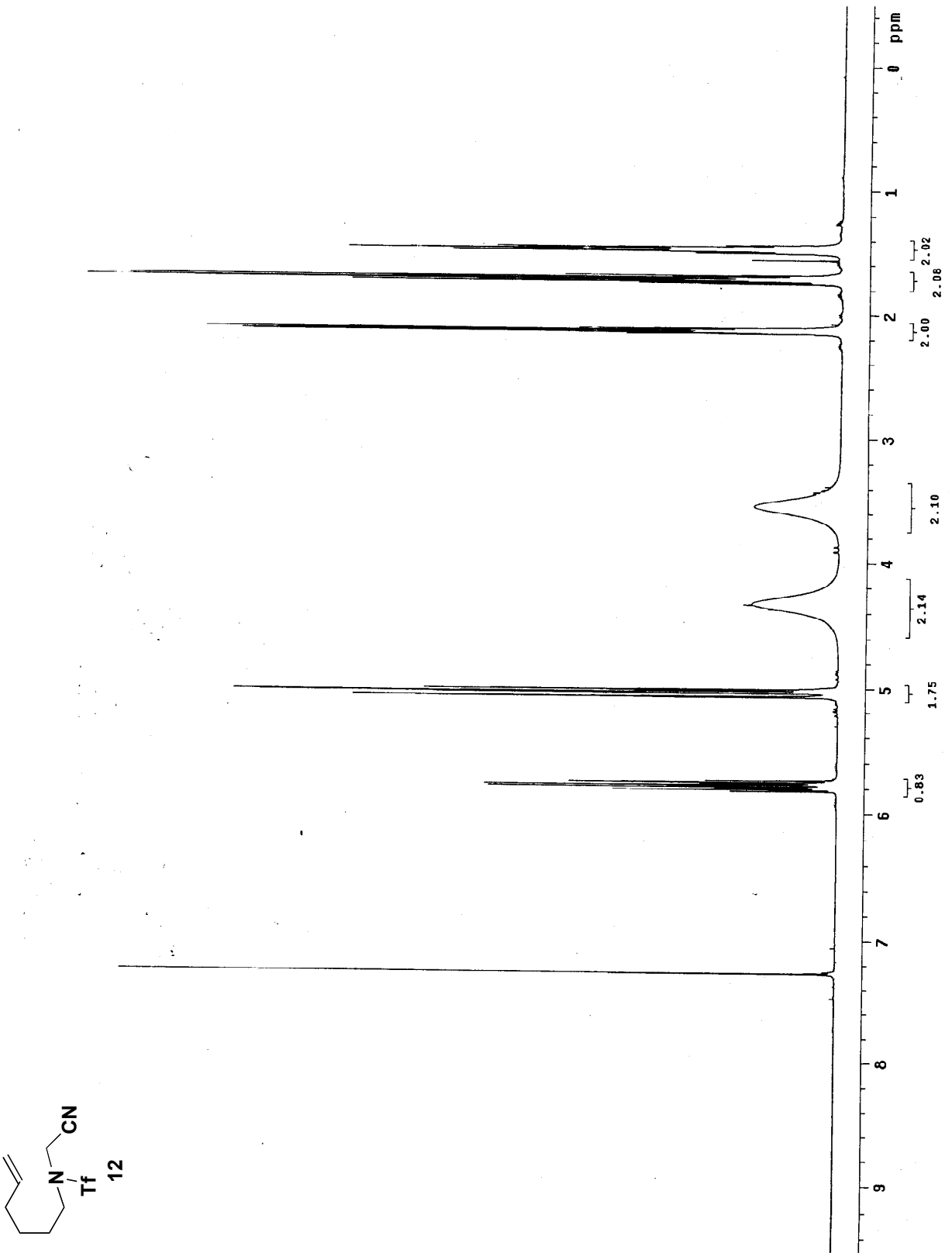
(1*R*, 4*S*, 9a*S*)-1-Methyldodecahydro-4-(*Z*)-(pent-2-en-4-ynyl)quinolizidine 217A (7). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with quinolizidine **26** (0.065 g, 0.29 mmol), $PdCl_2(PhCN)_2$ (0.011 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol), and 1 mL of piperidine. A solution of trimethylsilylacetylene (0.081 mL, 0.056 g, 0.57 mmol) in 1 mL of piperidine was added dropwise via cannula over 1 h and then the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with 15 mL of ether and 10 mL of 10% ammonium hydroxide solution. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.150 g of a black oil. This material was dissolved in 2 mL of CH_2Cl_2 and stirred with charcoal (0.150 g) and 3-mercaptopropyl-functionalized silica gel (0.150 g) at rt for 18 h. Filtration through a 1-in plug of Celite in a disposable pipette gave 0.104 g of an orange oil which was used immediately in the next step without further purification.

A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with K_2CO_3 (0.040 g, 0.29 mmol), 1.5 mL of MeOH, and the quinolizidine (0.104 g) prepared in the previous step. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 15 mL of diethyl ether. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated onto 0.5 g of silica gel. The free-flowing powder was placed at

the top of a column of 8 g of silica gel and eluted with 0-25% EtOAc-1% Et_3N-hexanes to provide 0.051 g (82%) of quinolizidine (–)-217A (**7**) as a yellow oil: $[\alpha]_D^{22}$ -14 (*c* 0.8, $CHCl_3$) [lit:[2] $[\alpha]_D^{22}$ -13.75 (*c* 0.4, $CHCl_3$)]; IR (film): 3312, 2973, 2852, 2784, 2097, 1615, 1452, 1376, 1264, 1127, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.10 (dt, J = 10.9, 7.1 Hz, 1 H), 5.48 (ddt, J = 10.9, 2.0, 1.6 Hz, 1 H), 3.29 (br d, J = 11.1 Hz, 1 H), 3.09 (d, J = 2.0 Hz, 1 H), 2.53-2.63 (m, 2 H), 2.05-2.10 (m, 1 H), 1.93 (br d, J = 11.9 Hz, 3 H), 1.02-1.79 (m, 12 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 109.6, 82.0, 81.0, 69.9, 63.4, 52.0, 36.7, 35.3, 34.2, 32.1, 30.5, 26.6, 25.0, 19.6; Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.83; H, 10.62; N, 6.42.

The enantiomeric purity of the product was determined by ^1H NMR analysis of the salt formed by reaction with (*R*)-(–)-1,1'-binaphthyl-2,2'-diylphosphoric acid:[2] the phosphoric acid (0.018 g, 0.051 mmol, 1.1 equiv) was added to a solution of **7** (0.010 g, 0.046 mmol) in ca. 0.7 mL of $CDCl_3$. The C-1 methyl group appeared as a doublet (J = 6.5 Hz) at 0.69 ppm; no doublet at 0.77 ppm could be detected. Similar analysis of racemic quinolizidine 217A showed two doublets (1:1 ratio) at 0.77 and 0.69 ppm.

[2] Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, 54, 5826.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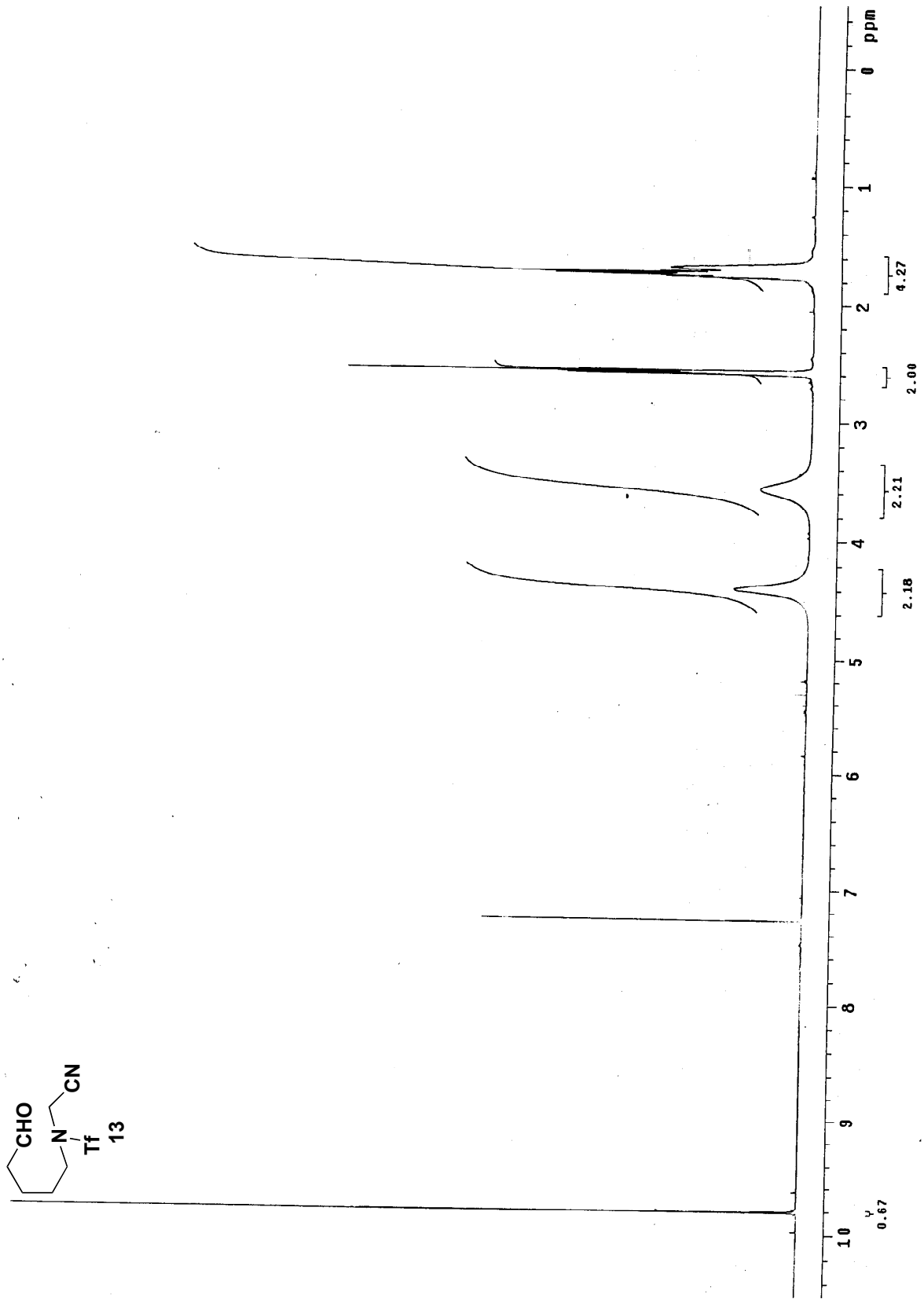
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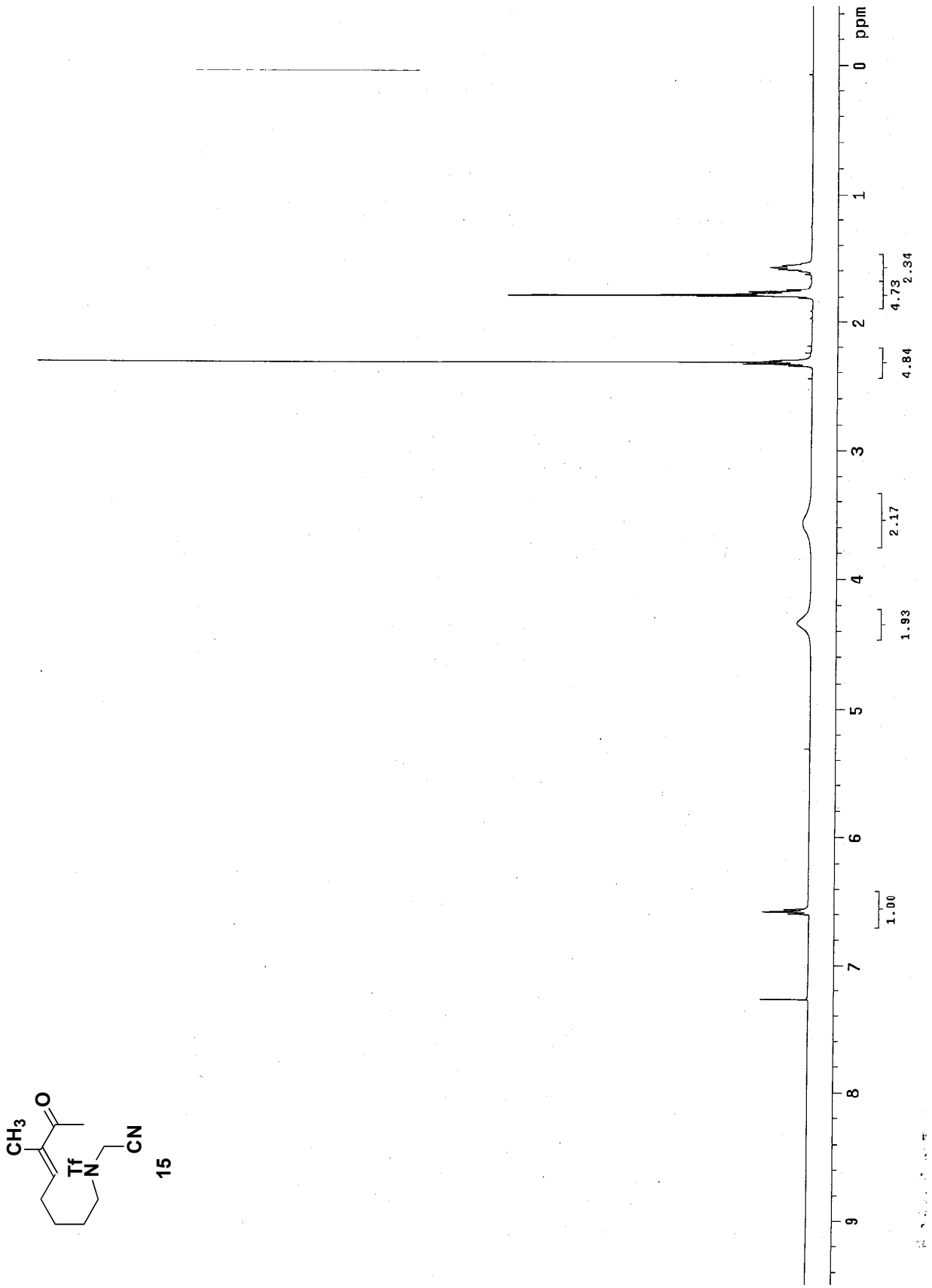
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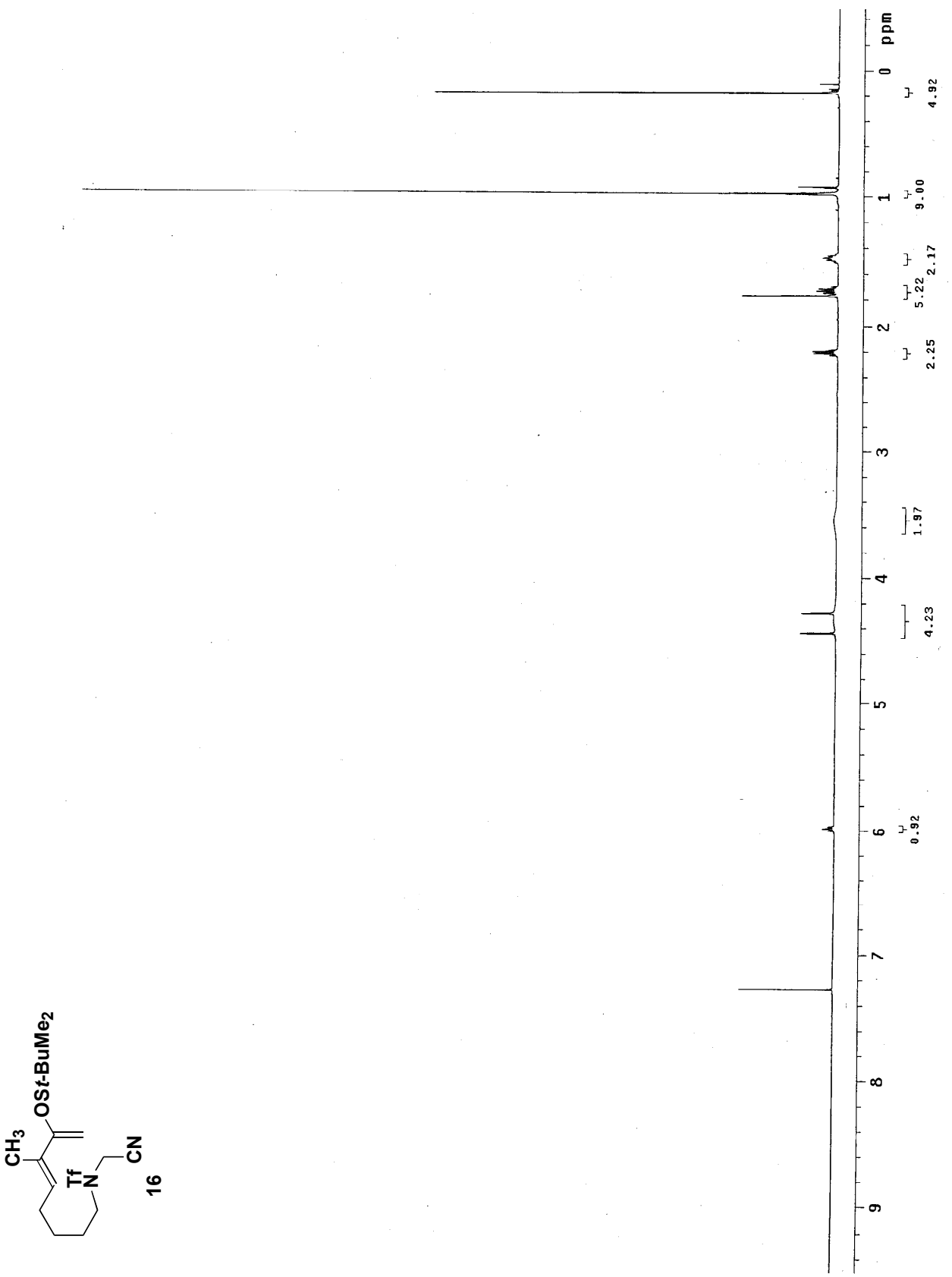
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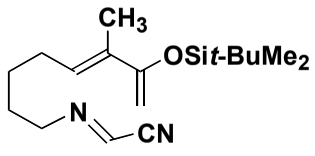
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CN

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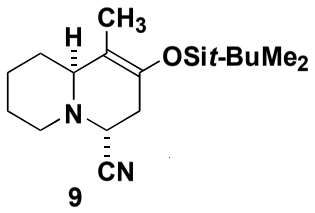
5.08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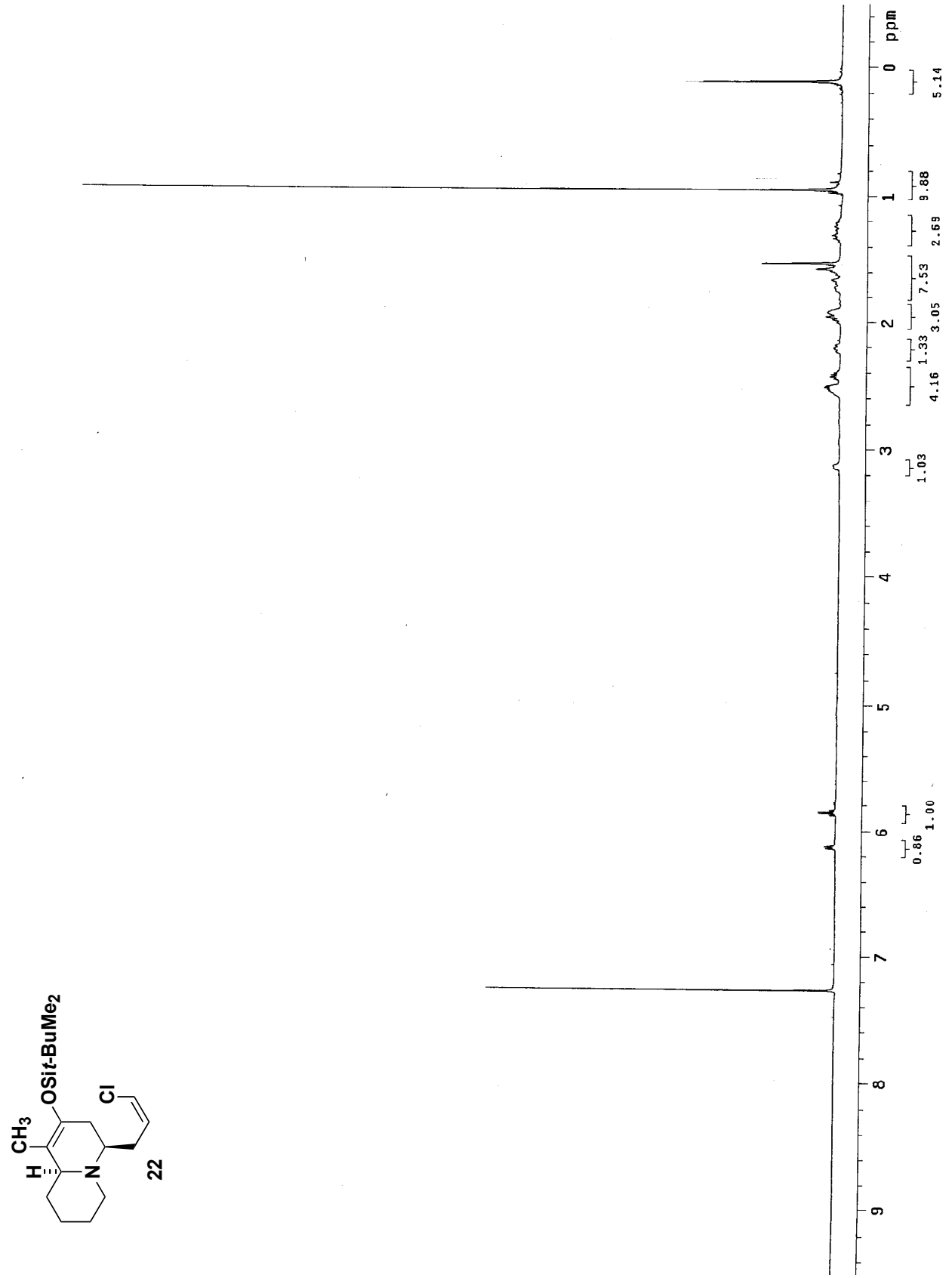
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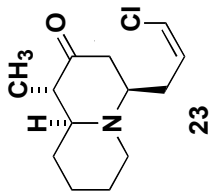
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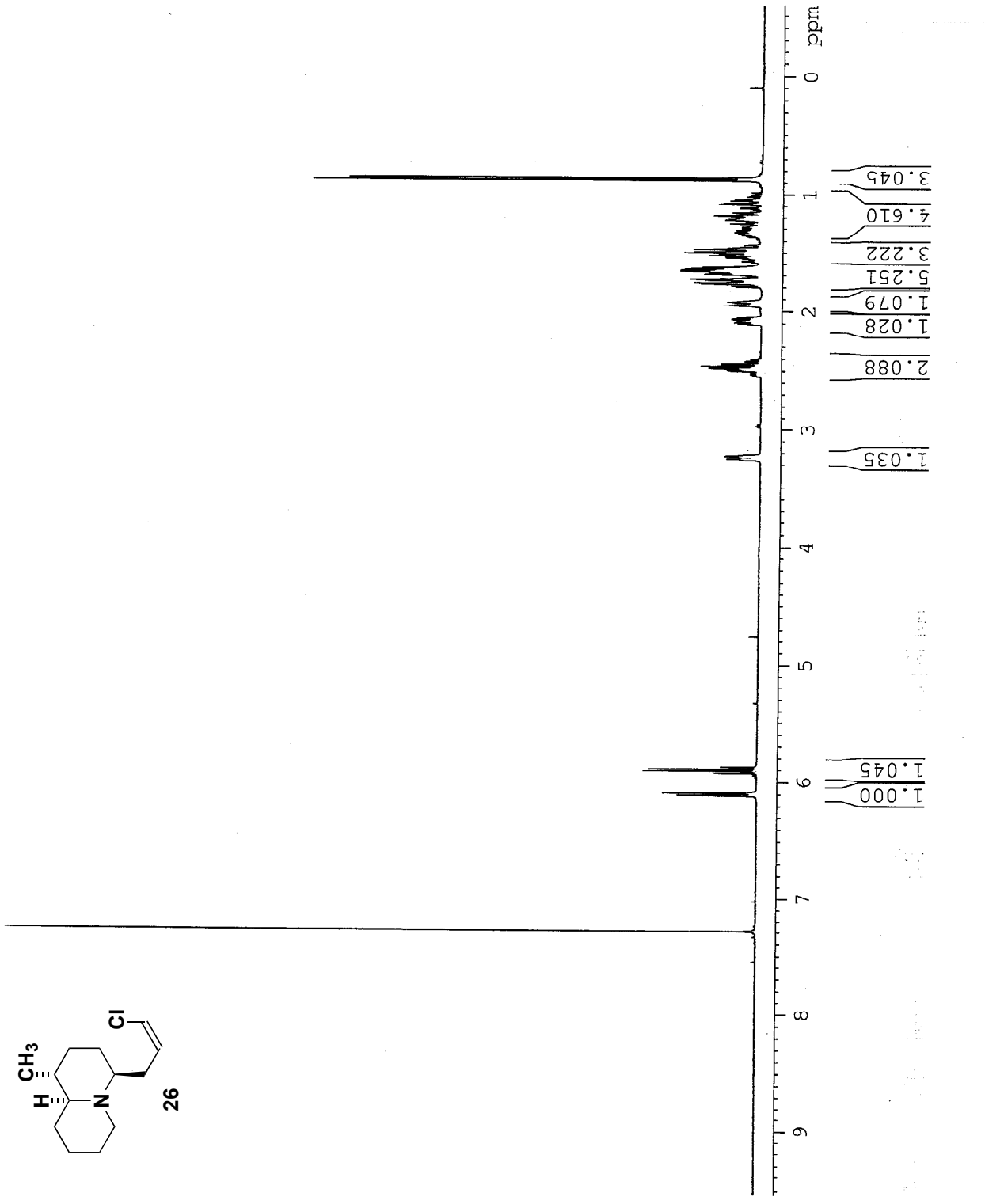
3.00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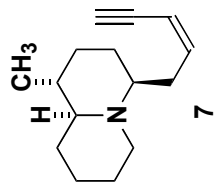
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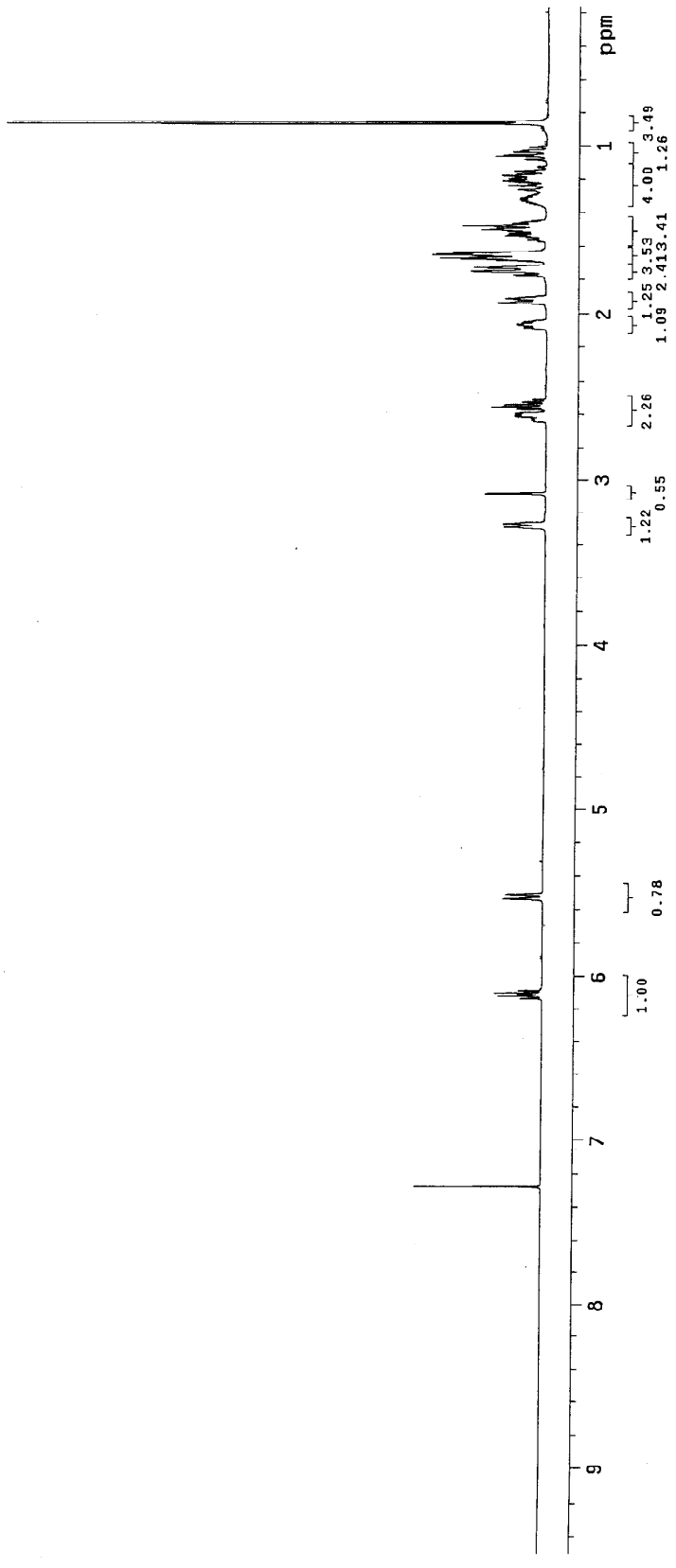
N

7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2.41
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3.49
1.26